REMARKS

Claims 79, 81 and 84-90 are pending in the subject application. Applicants have hereinabove cancelled claims 81, and 86-89 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in the future. Claims 86-89 were previously withdrawn from further consideration as drawn to nonelected inventions. In addition, applicants have amended claim 79. Accordingly, after entry of this Amendment claims 79, 84, 85 and 90, as amended, will be pending in this application.

Support for the amendments to claim 79 can be found in the specification as originally filed at, inter alia, page 7, lines 4-10; page 9, lines 9-11 and 30-32; page 18, lines 1-5; page 40, lines 29-31 (reciting osteoblasts); page 41, lines 7-27 (in particular lines 23-24); page 3, line 13, which indicates "CFU-F" is an abbreviation for "colony-forming-unit-fibroblast"; and page 42, lines 17-21.

Applicants maintain that the amendments made hereinabove raise no issue of new matter. Accordingly, applicants respectfully request entry of this Amendment.

Claims Rejected Under 35 U.S.C. §112, first paragraph (written description)

In the April 28, 2009 Final Office Action the Examiner rejected claim 81 under 35 U.S.C. §112, first paragraph (written description), asserting that the specification and claims as originally filed do not support "a method of generating a tissue, wherein a tissue is a mesenchymal tissue selected from the group recited in claim 81." The Examiner further objected to claim 81 asserting that it is dependent from cancelled claim 80.

In response, applicants have hereinabove cancelled claim 81 without disclaimer or prejudice to applicants' right to pursue the subject matter of this claim in the future. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected Under 35 U.S.C. §112, first paragraph (enablement)

In the April 28, 2009 Final Office Action the Examiner stated that claim 79 and claims dependent therefrom are rejected under 35 U.S.C. §112, first paragraph (enablement), asserting that the specification fails to enable the claimed subject matter. The Examiner asserted that the specification fails to adequately teach how to effectively generate any mesenchymal tissue in a subject by administering a population of STRO-1^{bright} cells. The Examiner further asserts that no animal models were used to study the effectiveness of STRO-1^{bright} cells in generating any mesenchymal tissues *in vivo*. The Examiner acknowledged applicants' previous arguments that the specification teaches administration of STRO-1^{bright} cells to a mouse model that resulted in the generation of bone lining cells, fibrous tissue and osteocytes having alu sequences of the human STRO-1^{bright} cells. However, the Examiner asserted that the specification clearly teaches that the "fat and smooth muscle cells surrounding the ceramic cubes did not express the alu sequence". The Examiner speculated that the observed human alu sequence could be the result of cell fusion between an endogenous cell and a STRO-1^{bright} cell or from an endogenous cell taking up DNA of a STRO-1^{bright} cell, based on the disclosures in Poulsom *et al., J. Am. Soc. Nephrol., 14*:s48-s54, 2003 and Holden *et al., Science 296*:2126-

2129, 2002. The Examiner also asserted that there is unpredictability in the art because:

(i) isolated stem cells are different to stem cells existing as part of the human body since maintaining stem cells *in vitro* requires stringent selection for proliferation and adaptation to tissue culture conditions (Hansson *et al., Stem Cells, 25*: 1507-1510, 2007); and

(ii) "in contrast to *in vitro* models, and partly animal-human xenograft systems, tissue cells *in vivo* seem to express molecules for defense against cellular immune systems as well as against complement. Although these defense mechanisms are still poorly understood, they provide some hints as to why many potential therapeutics perform marvelously *in vitro* but a fairly high portion them still fail *in vivo*." (Cochlovius *et al Modern Drug Discovery*, pages 33-38, 2003).

Finally, the Examiner asserted that the specification fails to provide any correlation between the *in vitro* data provided therein and administration of cells *in vivo*.

Applicants' Response

In response, applicants respectfully traverse the Examiner's objections. However, in order to expedite prosecution and without conceding the correctness of the Examiner's position, applicant notes that claim 79 has been amended hereinabove to recite a method of generating bone tissue.

Evidence of enablement

As to the Examiner's assertion that the specification fails to provide sufficient working examples to enable the invention, applicants direct the Examiner's attention to the specification. The Examiner has acknowledged that the disclosure at page 41, lines 16-36 teaches that *in vivo* implantation of ceramic cubes comprising human STRO-1^{bright} cells in mice resulted in the formation of cells having a human alu sequence and having the morphology of "fibrous tissue, bone lining cells and osteocytes." Although the Examiner has noted in the current Office Action that the fat and smooth muscle tissue surrounding the cubes was most likely of host mouse origin, this does not subtract from the fact that human bone lining cells and osteocytes were formed. Moreover, current claim 79 is directed to a method of generating bone tissue, not fat or smooth muscle tissue.

The Examiner's speculation that "fusion" may have occurred is based on a paper discussing renal tissue (Poulsom *et al.* 2003) which does not specifically discuss the problem with bone tissue. Applicants further note that the Examiner's speculation that "fusion" or "DNA uptake" may have occurred is also based on generalized assertions made in a review article (Holden *et al.* 2008, see page 2126 in particular), which discusses fusion and DNA uptake, but not in specific regard to bone tissue. Applicants note that the Examiner's assertion is merely speculation and note the Examiner has pointed to nothing in the specification to suggest fusion and/or DNA uptake has occurred here. In addition, the new fat, smooth muscle and vascular tissues observed in the working examples were found to have no human alu sequence (see page 41, line 34 to page 42, line 2). Accordingly, clearly no detectable fusion or DNA uptake occurred there.

In addition, post-filing art, described hereinbelow, supports the position that one skilled in the art following the teachings of the Specification with regard to the method as claimed would be able to perform the method without undue experimentation. Applicants submit the following documents describing results from *in vivo* studies:

(i) Fujii *et al., J. Cell. Physiol., 215*: 743-749, 2008 – (which is attached herewith as **Exhibit 8** of a Supplemental Information Disclosure Statement which is filed herewith), shows that implantation of human STRO-1$^+$ cells (but not human STRO-1$^-$ cells), isolated from periodontal ligament into mice results in the production of tissue expressing human osteocalcin, CP23, BSP and periostin mRNAs and human vimentin, periostin and osteocalcin expressing cells and PDL and bone tissue (pages 746 and 747, and Figures 3 and 4);

(ii) Yang *et al., Biochem. Biophys. Res. Comm., 342*: 1098-1107, 2006 (which is attached herewith as **Exhibit 18** of a Supplemental Information Disclosure Statement which is filed herewith), shows that implantation of STRO-1$^+$ cells into mice results in new bone formation. In particular, as discussed on page 1105, new bone formation is found within implanted scaffolds, which clearly cannot simply be explained by either fusion or DNA uptake; and

(iii) U.S. Serial No. 10/955,709 (co-pending related Published Application No. 2005-0158,289, published July 21, 2005; a copy of which was previously disclosed in a January 6, 2007 Information Disclosure Statement and considered by the Examiner on October 1, 2007) shows in Example 9 that

bone formation occurs in animals receiving autologous ovine STRO-1$^+$ cells.

Accordingly, the specification teaches, and post-filing publications submitted herewith demonstrate, that STRO-1 expressing MPCs are capable of generating bone tissue *in vivo*. Moreover, applicants' *in vivo* bone-generation model shows consistency with the post-filing publications. The Examiner's concern regarding *in vitro/in vivo* correlation is misplaced in light of applicant's demonstrated *in vivo* results. Accordingly, applicants maintain that the claims as amended are enabled and respectfully request that the Examiner reconsider and withdraw this ground of rejection.